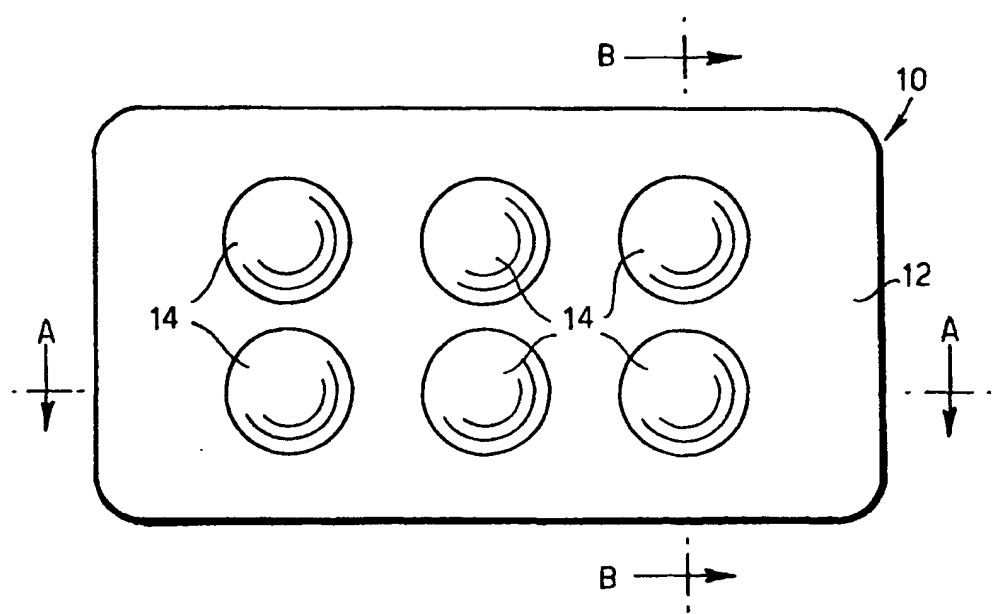


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>7</sup> : <b>A61K 9/48</b></p>	<p><b>A2</b></p>	<p>(11) International Publication Number: <b>WO 00/01372</b> (43) International Publication Date: 13 January 2000 (13.01.00)</p>
<p>(21) International Application Number: PCT/GB99/01851 (22) International Filing Date: 10 June 1999 (10.06.99) (30) Priority Data: 9814234.2 2 July 1998 (02.07.98) GB (71) Applicant (for all designated States except US): RECKITT &amp; COLMAN PRODUCTS LIMITED [GB/GB]; One Burlington Lane, London W4 2RW (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): JOLLIFFE, Ian [GB/GB]; 47 Kingsway, Cottingham, East Yorkshire HU16 5BB (GB). (74) Agent: DICKSON, Elizabeth, Anne; Reckitt &amp; Colman plc, Group Patent Dept., Dansom Lane, Hull HU8 7DS (GB).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published Without international search report and to be republished upon receipt of that report.</p>
<p>(54) Title: CHEWABLE ORAL UNIT DOSAGE</p> <div data-bbox="308 1134 1299 1743"></div> <p>(57) Abstract</p> <p>An oral unit dosage comprising a substrate defining a plurality of discrete reservoirs each containing a liquid fill for release in the mouth.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**CHEWABLE ORAL UNIT DOSAGE**

5 This invention relates to chewable capsules having improved acceptability for the consumer.

Soft gelatin capsules are a well established means for providing a variety of liquid products such as drugs or dietary supplements in a relatively  
10 digestible form.

EP 0211079 discloses a partitioned soft capsule in which a rapidly soluble film is used to form both parts of a capsule. The capsule is able to deliver two  
15 separate liquid compositions which are contained within separate but adjacent reservoirs in the capsule to the mouth. The capsules of this patent suffer the disadvantage that they are not easy to grip between the teeth when chewing and are thus prone to "popping  
20 out" from between the teeth as the patient bites the capsule. In addition, it is necessary to form the capsule from at least three separately fed sheets of material thereby increasing the complexity of manufacture and hence the cost per capsule.  
25

When chewable capsules are chewed or bitten (rather than swallowed), they release their contents into the mouth. This may be particularly advantageous when the capsule contents have a topical effect in the mouth or  
30 throat or when the liquid fill provides a soothing or coating effect. Delivering liquids by this means is particularly useful when bulk doses of liquid medicaments are not convenient (e.g. because of frequent or irregular dosing patterns or when  
35 measuring doses accurately is not convenient).

Chewable capsules may also be particularly advantageous when the patient is unable or unwilling to swallow solid dosage forms (e.g. tablets or hard capsules) e.g. because of age, throat  
5 pain/constriction etc.

The full commercial development of such chewable dosage forms has however been hindered by two  
10 particular drawbacks.

Firstly, for capsules above a volume of approximately 0.5 ml, when the capsule is bitten the resulting burst of contents is aesthetically unpleasant, indeed it has been likened to "biting an  
15 eyeball". To overcome this drawback it has been suggested that the fill volume of the capsules should be reduced, but this is not always practical. To reduce the fill volume whilst delivering the same drug dosage the fill must be more concentrated, which in  
20 most cases means more viscous. Increasing viscosity leads to difficulty in filling the capsules accurately (as the fill must be pumped through narrow dosing tubes) and consequent unacceptable dose variations. Also small capsules are difficult to locate between  
25 the teeth and are therefore difficult to break open.

A second disadvantage of conventional chewable capsules is that many active materials or excipients are incompatible with each other when combined in a  
30 liquid fill. This incompatibility may be due to reactions between two or more components of the liquid fill, leading to e.g. degradation of one or more of the active materials, or the release of gases which cause the capsules to burst. This means that for many  
35 combinations of active materials and or excipients it is necessary to provide two or more different capsules

each time a dose is taken; increasing the risk of confusion of the patient and poor compliance with the correct dosing schedule.

5        There is thus a need for a chewable capsule which is capable of delivering one or more liquid compositions to the mouth without the unpleasant sensation of the contents spurting out that occurs when a conventional capsule is bitten. It is also desirable for the  
10        chewable capsule to be suitable for delivering two or more incompatible liquid formulations to the patient via a single oral dosage form. Ideally, the chewable capsules should have a simple construction and be inexpensive to manufacture. The present invention  
15        aims to provide a chewable capsule satisfying the above aims and having a mouth feel which is acceptable to the patient.

20        According to the present invention there is provided a chewable oral unit dosage for releasing liquid in the mouth, comprising a soft ingestible substrate which includes a plurality of spatially-separated reservoirs, wherein each reservoir is adapted to retain liquid fills, preferably discrete liquid fills,  
25        and wherein the release of the liquid fills from the reservoirs occurs in a controlled manner when the unit dosage is chewed.

30        Preferably the oral unit dosage is a capsule, more preferably a gelatin capsule.

35        By controlled manner it is meant that, whether or not more than one liquid fill composition is used in the same capsule, the normal liquid fill volume is divided between a number of smaller reservoirs with the result that only a few reservoirs are burst in any

one bite and the sudden burst of a large volume of liquid fill will be avoided.

5 The individual discrete reservoirs are non inter-connecting and are spaced apart from one another.

Preferably in the oral unit dosages of the invention each reservoir has substantially the same volume.

10 Preferably the volume of each of the reservoirs in the oral unit dosages of the invention is not more than 0.5 ml, more preferably it is from 0.05 to 0.5 ml and most preferably from 0.1 to 0.35 ml.

15 Preferably the substrate of the oral unit dosages of the invention comprise from 2 to 30 reservoirs, more preferably from 5 to 20, and most preferably from 10 to 15.

20 Optionally the oral unit dosages of the invention may contain at least two different liquid fills in different reservoirs. The different liquid fills may separately contain components that would be incompatible if they were combined in a single liquid  
25 fill, for example two incompatible active materials or an active material and an incompatible excipient.

Examples of incompatible components include acids and bases; for example alginic acid and sodium  
30 bicarbonate, cetylpyrrolidinium chloride and ascorbic acid, cimetidine and sodium bicarbonate, effervescent couples (e.g. citric acid and sodium bicarbonate), aspartame (a sweetener) and magnesium trisilicate (an  
35 antacid), cimetidine and vanilla (a flavouring agent), or benzocaine and cherry flavour.

It is possible in the oral unit dosages of the invention that the walls of the reservoirs are composed of a different material from the substrate in which they are embedded. However, it is preferred  
5 that the reservoir walls are composed of the same material as the substrate, i.e. the reservoirs are merely spaces in the substrate produced by the insertion of and/or including the liquid fill(s).

10 Thus, the oral unit dosages of the invention preferably consist essentially only of two components, the substrate and one or more liquid fills plus, optionally, a coating agent.

15 The substrate may comprise any film-forming material suitable for forming chewable capsules, for example suitably treated starch, cellulose or derivatives thereof or gelatin. Preferably the substrate comprises gelatin.

20

The substrate may further comprise agents to improve its handling or organoleptic properties, for example plasticisers (e.g. glycerine, sorbitol or propylene glycol, in amounts of up to 50%, more preferably 20-  
25 35%, by weight of the substrate); water (up to 50%, more preferably 30-40%, by weight of the substrate); preservatives (e.g. potassium sorbate or methyl, ethyl or propyl parabens); dyes; opacifiers; flavours; or additional drug substances.

30

The liquid fill will comprise either a solid active material that has been dissolved, solubilised, or dispersed (with suspending agents such as beeswax, hydrogenated castor oil or polyethylene glycol 4000),  
35 or a liquid active material; in vehicles or combinations of vehicles such as mineral oil,

vegetable oils, triglycerides, glycols, polyols, and surface active agents.

5 The liquid fill may optionally also comprise  
flavouring agents, sweeteners or powdery materials to  
improve the mouth feel of the fill once the reservoirs  
are broken open (e.g. bulk sweeteners such as sucrose  
or mannitol).

10 The selection of appropriate substrate materials  
plus excipients and fill materials will be obvious to  
one skilled in the art of chewable capsule production,  
and will depend largely upon the active material  
being delivered by the oral unit dosage of the  
15 invention.

It will be appreciated that, when the amount of fill  
material dosed into each reservoir is fairly low,  
care should be taken to ensure that the fill is not  
20 too viscous for accurate dosing. This will not be  
such a problem as in the production of single low  
volume capsules as the concentration of active agent  
will not need to be so high as in such capsules.

25 Suitable active materials for use in the oral unit  
dosages of the invention include any materials that  
may be formulated in a liquid fill, for example:

30 a) systemically acting agents, such as histamine  
H<sub>2</sub> receptor antagonists (e.g. ranitidine),  
proton pump inhibitors (e.g. omeprazole),  
prokinetic agents (e.g. metoclopramide),  
antidiarrhoeal agents (e.g. loperamide),  
laxatives (e.g. senna powder), non seroidal  
35 anti-inflammatory agents (e.g. naproxen,  
diclofenac, ibuprofen and aspirin) or  
decongestants (e.g. pseudoephedrine);



- b) materials acting locally in the mouth, such as local antimicrobial agents (e.g. cetyl pyridinium chloride, hexyl resorcinol, triclosan), local anaesthetics (e.g. lignocaine hydrochloride, benzocaine), anti-inflammatory agents (e.g. aspirin, benzydamine, ketoprofen), steroids (e.g. hydrocortisone), topical antibiotics (e.g. tyrothricin, fusafungine, nystatin), decongestants (e.g. phenylephrine hydrochloride) or anti-histamines (e.g. terfenadine);
- c) materials acting locally in the throat or oesophagus, such as cough suppressants (e.g. dextromethorphan), expectorants (e.g. guaiaphenesin), antacids (e.g. calcium carbonate, sodium bicarbonate), or soothing/coating agents (e.g. sodium alginate or dimethicone).

Suitable materials that may optionally be used to coat the oral unit dosages of the invention include cellulose derivatives such as hydroxy ethyl cellulose, hydroxy methyl cellulose or hydroxy propyl cellulose.

The oral unit dosages of the invention may be manufactured by any of the methods normally used for the production of chewable capsules having low fill volumes (taking into account the materials selected), with the special adaptation that the encapsulated dosages are not separated individually but are divided up so that each dosage comprises a plurality of discrete reservoirs. The method of manufacture may be further adapted so that each of the individual reservoirs has a volume of less than 0.5 ml and/or so that two or more different liquid fills are included

in different reservoirs within the same oral unit dosage.

Commercial methods for producing chewable capsules include the plate process and the rotary die encapsulation process.

Example of the use of both the plate process and rotary die encapsulation machines are given in, for example, Soft Gelatin Capsules: A Solution To Many Tableting Problems by H. Seager in Pharmaceutical Technology, September 1985, 84-104; and Soft Gelatin Capsules by J. P. Stanley in Theory and Practice of Industrial Pharmacy Eds Lachman L, Lieberman HA, König J L, 405-420, 1976.

The invention will now be described with reference to the following non-limiting illustrations in which:

Figure 1 is plan view of an oral unit dosage according to the invention;

Figure 2 is an side view cross section (A-A) of an oral unit dosage according to the invention; and

Figure 3 is a end view cross section (B-B) of an oral unit dosage according to the invention;

In the Figures, the oral unit dosage includes a flat gelatin laminate 12 consisting of two separate gelatin cards 12A and 12B laminated together. The gelatin laminate 12 includes six discrete, sealed, reservoirs 14 which are non-interconnecting and are spaced apart from one another. Each reservoir 14 is filled with liquid fill 16.

When the unit dosage is chewed, only a few reservoirs will burst yielding their liquid fill in any one bite

with the result that a sudden burst of a large volume of liquid fill is avoided.

The invention will now be illustrated by reference to the following examples:-

Example 1 .

	<u>Liquid Fill</u>	<u>mg Per Capsule</u>
10	Calcium Carbonate	500
	Sodium Bicarbonate	100
	Fractionated Coconut Oil	600
	Lecithin	12
15	Colloidal Silicon Dioxide	34
	Sorbitan Fatty Esters	34
	Polysorbate 80 BP	20
	Flavours/Colours/Sweeteners	80
20		----- 1380 mg (1.2ml)

	<u>Capsule Material</u>	<u>% by Weight</u>
	Gelatin	40
	Glycerin	25
25	Water	35
	Mint Flavour	qs
	Sweetener	qs
	Colour	qs

30        The oral unit dosages are prepared on a conventional rotary die encapsulation machine adapted to provide an individual fill volume of 0.1 ml; and further adapted so that the encapsulated reservoirs are not individually cut off but are divided up in blocks of  
35        12 reservoirs i.e. each oral unit dosage comprises a single piece of gelatin defining twelve reservoirs each having a liquid fill of 0.1 ml.

The resultant chewable capsules deliver an antacid material to the throat and oesophagus without the "chalky" characteristics normally associated with conventional antacid tablets. The capsules are pleasant to chew and do not produce an unpleasant burst effect upon biting.

Example 2

10

Liquid Fill 1

mg per capsule

	Calcium carbonate	100
	Sodium bicarbonate	100
15	Lecithin	12
	Fractionated coconut oil	600
	Colloidal silicon dioxide	34
	Sorbitan fatty ester	34
	Poly sorbate 80	20
20	Flavours/Colours/Sweeteners	80
		1380 mg (1.2 ml)

Liquid Fill 2

mg per capsule

25

	Alginic acid	500
	Lecithin	12
	Fractionated coconut oil	600
	Colloidal silicon dioxide	34
30	Sorbitan fatty esters	34
	Polysorbate 80	20
	Flavours/Colours/Sweeteners	80
		1380 mg (1.2 ml)

35

Capsule Material

As example 1

11

The oral unit dosages are prepared as in Example 1 with the further adaptation that the two liquid fills are delivered separately to the capsules, such that each oral unit dosage comprises a single piece of  
5 gelatin defining twelve reservoirs each of 0.1 ml volume, six of the reservoirs containing liquid fill 1 and six containing liquid fill 2.

Two capsules of Example 2 provide a full dose of  
10 alginic acid which will form a raft on contact with the stomach contents to treat heartburn, gastritis or dyspepsia.

When chewed the capsules of Example 2 have a  
15 pleasant mouth feel and do not give a sudden unpleasant burst of fill material.

Claims

1. A chewable oral unit dosage for releasing liquid  
5 in the mouth, comprising a soft ingestible  
substrate which includes a plurality of spatially-  
separated reservoirs, wherein each reservoir is  
adapted to retain liquid fills and wherein release  
10 of the liquid fill from the reservoirs occurs in a  
controlled manner when the unit dosage is chewed.
2. An oral unit dosage as claimed in claim 1,  
wherein the plurality of reservoirs contains two  
or more different liquid fills.  
15
3. An oral unit dosage as claimed in claim 1 or 2,  
wherein the volume of each reservoir is not more  
than 0.5ml, preferably from 0.05 to 0.5ml, most  
preferably from 0.1 to 0.35ml.  
20
4. An oral unit dosage as claimed in claim 1, 2 or  
3, wherein the substrate comprises from 2 to 30  
reservoirs, preferably from 5 to 20 reservoirs,  
and most preferably from 10 to 15 reservoirs.  
25
5. An oral unit dosage as claimed in any preceding  
claim, wherein the substrate comprises an  
ingestible film-forming material, and preferably  
wherein the reservoir walls are composed of the  
30 same material as the substrate.
6. An oral unit dosage as claimed in claim 5,  
wherein the film-forming material is gelatin.

7. An oral unit dosage as claimed in any preceding claim, wherein the liquid composition includes one or more active agents selected from:

- 5           a) Systematically active agents, such as histamine  
            H<sub>2</sub> receptor antagonists (e.g. ranitidine),  
            proton pump inhibitors (e.g. omeprazole),  
            prokinetic agents (e.g. metoclopramide),  
            antidiarrhoeal agents (e.g. loperamide)  
10           laxatives (e.g. senna powder), non steroidal  
            anti-inflammatory agents (e.g. naproxen,  
            diclofenac, ibuprofen and aspirin)  
            decongestants (e.g. pseudoephedrine);
- 15           b) Materials acting locally in the mouth such as  
            local antimicrobial agents (e.g. cetyl  
            pyridinium chloride, hexyl resorcinol,  
            triclosan), local anaesthetics (e.g. lignocaine  
            hydrochloride, benzocaine), anti-inflammatory  
20           agents (e.g. aspirin, benzydamine, ketoprofen),  
            steroids (e.g. hydrocortisone), topical  
            antibiotics (e.g. tyrothricin, fusafungine,  
            nystatin), decongestants (e.g. phenylephrine  
            hydrochloride), anti-histamines (e.g.  
25           terfenadine);
- c) Materials acting locally in the throat or  
            oesophagus such as cough suppressants (e.g.  
            dextromethorphan), expectorants (e.g.  
30           guaiphenesin), antacids (e.g. calcium  
            carbonate, sodium bicarbonate), and  
            soothing/coating agents (e.g. sodium alginate  
            or dimethicone).
- 35           8.    An oral unit dosage as claimed in any preceding  
            claim, wherein the substrate further comprises one

or more of: plasticisers, water, preservatives, dyes, opacifiers, flavours, additional active agents, and sweeteners.

- 5        9.    An oral unit dosage as claimed in claim 7 or 8, wherein the active agents in the liquid composition are dissolved, solubilised, emulsified, and/or dispersed.
- 10       10.   An oral unit dosage substantially as hereinbefore described with reference to the examples.



1/1

Fig.1.

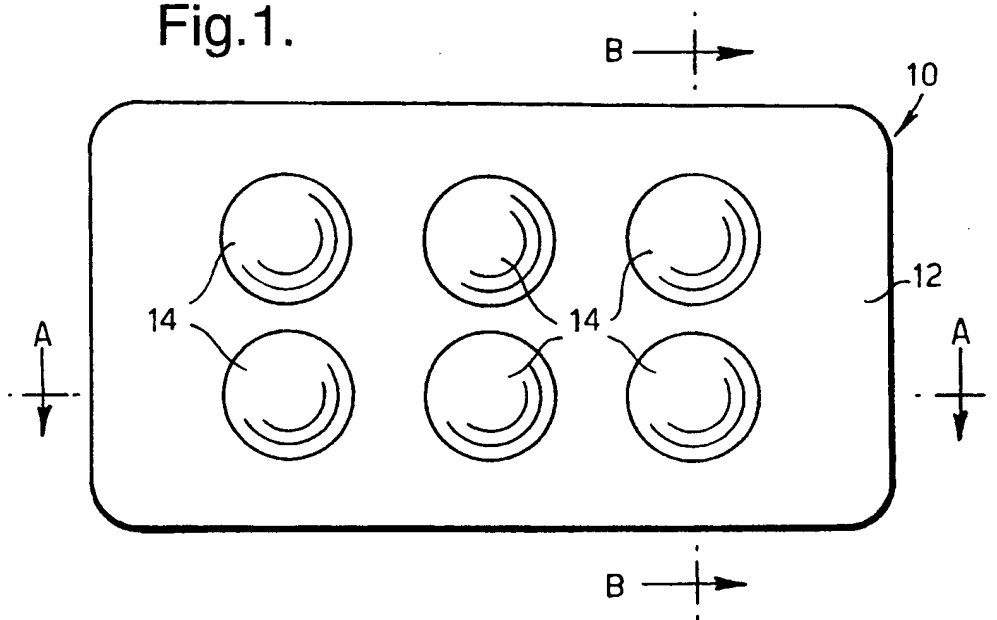


Fig.2.

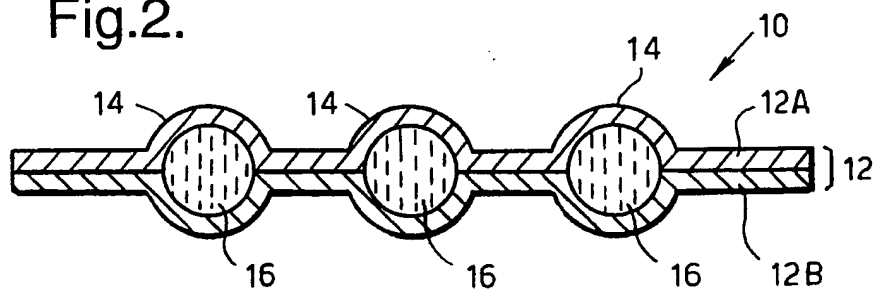
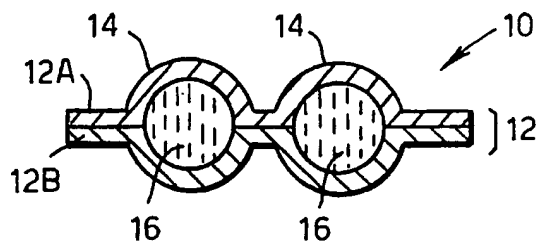


Fig.3.



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>7</sup> : <b>A61K 9/48</b></p>	<p><b>A3</b></p>	<p>(11) International Publication Number: <b>WO 00/01372</b> (43) International Publication Date: 13 January 2000 (13.01.00)</p>
<p>(21) International Application Number: PCT/GB99/01851 (22) International Filing Date: 10 June 1999 (10.06.99) (30) Priority Data: 9814234.2 2 July 1998 (02.07.98) GB (71) Applicant (for all designated States except US): RECKITT &amp; COLMAN PRODUCTS LIMITED [GB/GB]; One Burlington Lane, London W4 2RW (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): JOLLIFFE, Ian [GB/GB]; 47 Kingsway, Cottingham, East Yorkshire HU16 5BB (GB). (74) Agent: DICKSON, Elizabeth, Anne; Reckitt &amp; Colman plc, Group Patent Dept., Dansom Lane, Hull HU8 7DS (GB).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p> <p>(88) Date of publication of the international search report: 24 February 2000 (24.02.00)</p>
<p>(54) Title: CHEWABLE ORAL UNIT DOSAGE</p> <div data-bbox="316 1134 1291 1743"> </div> <p>(57) Abstract</p> <p>An oral unit dosage comprising a substrate defining a plurality of discrete reservoirs each containing a liquid fill for release in the mouth.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

# INTERNATIONAL SEARCH REPORT

**International Application No.**

PCT/GB 99/01851

### A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 148 841 A (WARNER LAMBERT CO) 5 June 1985 (1985-06-05) page 1, line 5 - line 21 page 2, line 80 - line 94 page 2, line 114 - line 125 page 3, line 103 - line 122 ---	1-10
X	EP 0 308 637 A (STEPHAN DIETER ;STEPHAN GUENTER (DE)) 29 March 1989 (1989-03-29) column 1, line 31 - line 53 column 3, line 8 - line 34 ---	1,2,4-6, 8-10
X	DE 19 65 257 A (LTS LOHAMNN THERAPIE SYSTEME GMBH) 8 July 1971 (1971-07-08) column 1, line 3 - line 8 column 2, line 48 -column 3, line 1 column 3, line 53 - line 62 ---	1-3,5,7, 9,10
	---	

**X**

Further documents are listed in the continuation of box C.

**X**

Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

**"&" document member of the same patent family**

Date of the actual completion of the international search

7 January 2000

Date of mailing of the international search report

14/01/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

**Authorized officer**

Boulois, D

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 99/01851

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP 0 211 079 A (FUJISAWA PHARMACEUTICAL CO) 25 February 1987 (1987-02-25) cited in the application the whole document</p> <p>-----</p>	1-10

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/01851

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2148841 A	05-06-1985	BE 900950 A	30-04-1985
		CH 661878 A	31-08-1987
		DE 3438656 A	23-05-1985
		FR 2554418 A	10-05-1985
		IT 1178193 B	09-09-1987
		JP 1947556 C	10-07-1995
		JP 6073539 B	21-09-1994
		JP 60132562 A	15-07-1985
		US 4738724 A	19-04-1988
		US 4738817 A	19-04-1988
EP 0308637 A	29-03-1989	DE 3727894 A	02-03-1989
		DK 457288 A	22-02-1989
		FI 883785 A	22-02-1989
		NO 883667 A	22-02-1989
DE 1965257 A	08-07-1971	NONE	
EP 0211079 A	25-02-1987	WO 8604501 A	14-08-1986